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(57) Abstract

The invention concerns C-glycosylated derivatives of soft carbon nucleophile compounds, particularly compounds which contain acid-labile structural units. The invention further concerns a mild, cost-effective, non-hazardous and stereoselective method of general application employing a glycal as a glycosylating agent and iodine as a catalyst for the preparation of C-glycosylated soft carbon nucleophile compounds.

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SYNTHESIS OF C-GLYCOSYLATED COMPOUNDS WITH THE USE OF A MILD, IODINE-CATALYZED REACTION

Field of the Invention

The invention concerns C-glycosylated derivatives of soft carbon nucleophile compounds, particularly compounds which contain acid-labile structural units, and more particularly, C-glycosylated derivatives of known compounds that are useful pharmacological agents such as antibiotics, antineoplastic compounds and antiviral compounds. The invention further concerns a mild, cost-effective, non-hazardous and stereoselective method of general application employing a glycal as a glycosylating agent and iodine as a catalyst for the preparation of C-glycosylated soft carbon nucleophile compounds.

Background of the Invention

A large number of drugs that exhibit potent antibiotic, antitumor and/or antiviral activity belong to the structural class of compounds known as C-glycosides, in which a carbohydrate moiety is attached to a carbon atom of a typically hydrophobic aglycon unit. Although their glycons are not particularly hydrophobic, C-nucleosides are the most representative of these C-glycosides both in their abundance and in their biological activities. Numerous C-glycosides are currently on the market as medicinal drugs. Therefore, development of an improved method for the synthesis of such compounds, especially their structural analogs that may possess enhanced pharmacological profiles, continues to be an area of intense commercial interest in the pharmaceutical and chemical industry (for reviews, see: Hacksell, U.; Daves, G.D., Jr. *Prog.Med.Chem.* 1985, 22,1-65 and Daves, G.D., Jr. *Acc.Chem.Res.* 1990, 23, 201-206

both incorporated herewith by reference).

While several reactions that utilize glycal derivatives as glycosylating reagents have been reported employing various Lewis acids as catalysts for C-glycosylation, the harsh nature of these Lewis acids has prevented their application to the synthesis of the C-glycosylated derivatives of acid-labile substrates. These Lewis acids include boron trifluoride etherate (Dawe, R.D.; Fraser-Reid, B. *J.C.S.Chem.Commun.*1981, 1180-1181; Panek, J.S.; Sparks, M.A. *J.Org.Chem.* 1982, 47, 3805-3806; Sabol, J.S.; Cregge, R.J. *Tetrahedron Lett.* 1989, 30, 6271-6274), ethyldichloroaluminum, and trimethylsilyl trifluoromethanesulfonate (for the use of both of these Lewis acids, see: Herscovici, J.; Muleka, K.; Antonakis, K. *Tetrahedron Lett.* 1984, 25, 5653-5656). In addition, since most of these strong Lewis acids spontaneously react with air and moisture, the use of these Lewis acids presents serious problems in their handling, particularly under the large-scale, industrial setting. Another approach to C-glycosylation that employs a glycal derivative requires the use of expensive metal catalyst whose effects to human health could potentially be serious drawbacks (Hacksell, U.; Daves, G.D., Jr. *J.Org.Chem.* 1983, 48, 2870-2876).

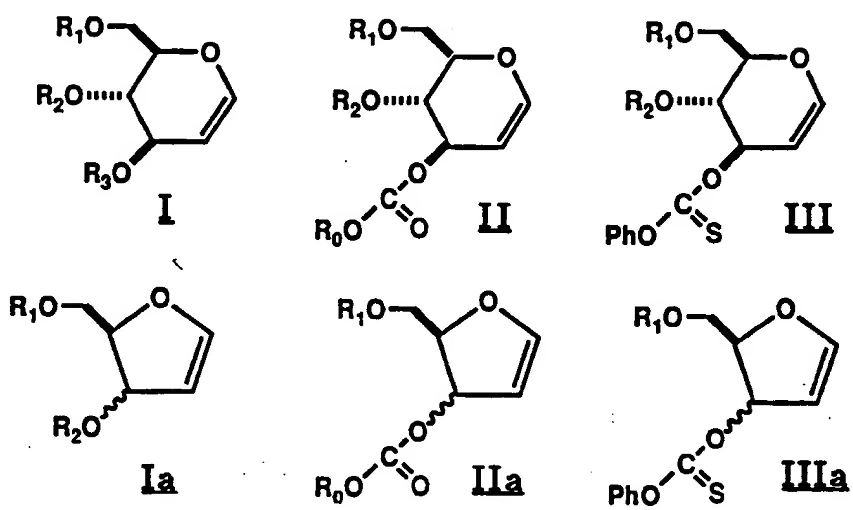
Summary and Detailed Description

In one preferred aspect, the invention concerns C-glycoside compounds, as C-1α and C-1β epimer compounds, obtained by reacting a soft carbon nucleophile compound and a glycosylating agent selected from 3-acylated, carbonated and thionocarbonated five- and six-membered glycals in the presence of a catalytic amount of iodine (5-50 mol% with 20 mol% being the most representative) to provide a reaction

mixture containing the corresponding C-1α and C-1β C-glycoside epimers, isolating at least one or both of said α and β epimers stereoselectively from said mixture, and optionally removing one or more acyl groups from said epimer products.

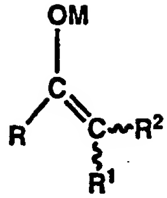
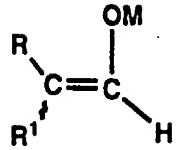
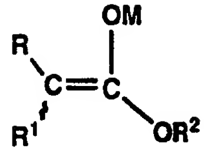
The use of the non-toxic, stable catalyst iodine, which is an extremely mild Lewis acid and yet according to the invention retains enough acidity to effect C-glycosylation, has virtually solved the heretofore difficult problems of the art.

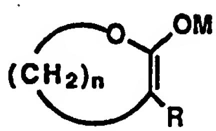
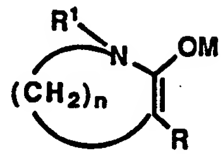
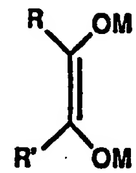
For glycosylation, glycals of the formulas I-III and Ia-IIIa are preferred:

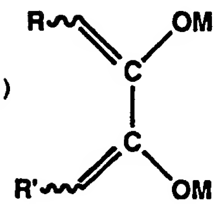
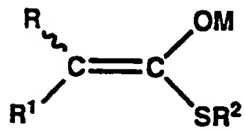
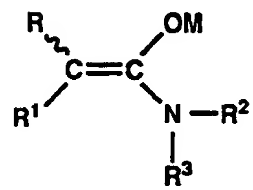


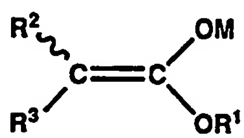
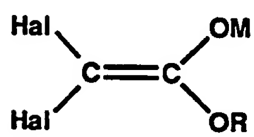
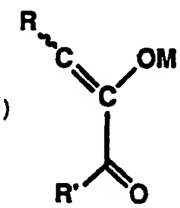
where R_0 is a lower alkyl group and R_1, R_2 and R_3 are the same or different and represent an aliphatic acyl group or an aromatic acyl group such as a benzoyl group. The glycals are commonly available or can be prepared by known methods.

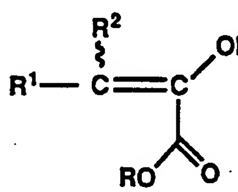
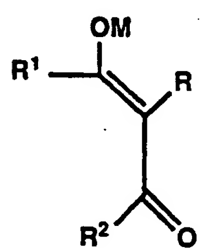
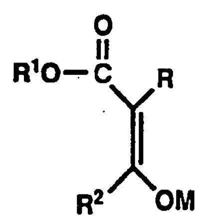
Preferred soft carbon nucleophiles comprise a compound or a moiety selected from members of the group consisting of enolate derivatives having the formulas a) to w)

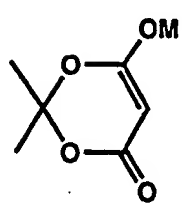
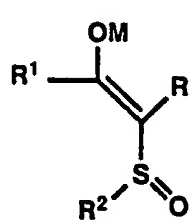
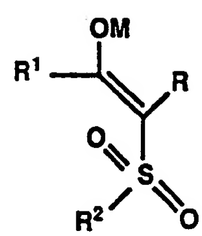
a)  ; b)  ; c)  ;

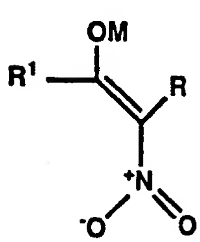
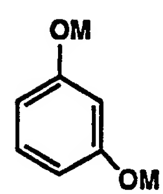
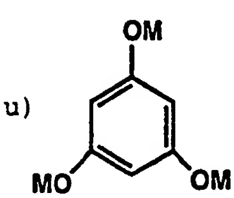
d)  ; e)  ; f)  ;

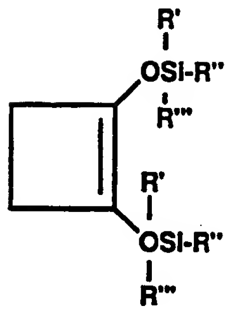
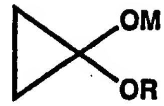
g)  ; h)  ; i)  ;

j)  ; k)  ; l)  ;

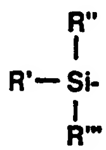
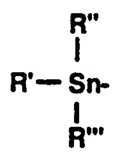
m)  ; n)  ; o)  ;

p)  ; q)  ; r)  ;

s)  ; t)  ; u)  ;

v)  ; and w)  ;

and allyl, vinyl, alkynyl and propargyl silanes and stannanes, and MCN; wherein M represents

 or  ,

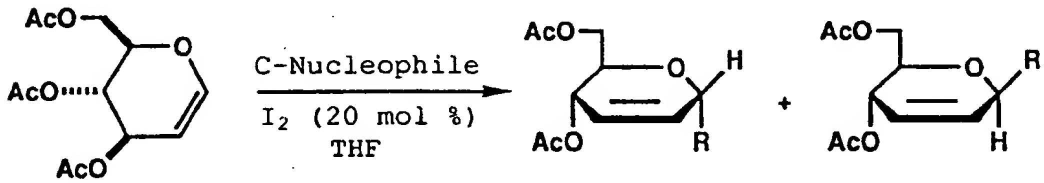
R, R^1 and R^2 are independently selected from alkyl, aryl, alkenyl and alkynyl, n is from 1 to 5, Hal is a halogen atom, and R′, R″ and R‴ are independently selected from lower alkyl groups. Preferred nucleophiles are precursors of showdomycin, ravidomycin, formycin, and analogs thereof.

Thus, the soft nucleophiles include derivatives of enolates of ketone, aldehyde, ester, lactone, thioester, amides, and lactams, generally represented as RO-C(X)=C where X is a substituent and R is a trialkyl, dialkylaryl, and alkyldiaryl, or triarylsilyl or tin group, ketene acetals, 1,2- and 1,3-dicarbonyl compounds including Meldrum's acid and their derivatives, β-ketosulfoxides, β-ketosulfones, and β-ketonitro compounds and their derivatives, allyl, vinyl, aryl, alkynyl, and propargyl silanes and stannanes, silyl and stannyl cyanides (RR′R″SiCN and RR′R″SnCN), 1,3- and 1,3,5-dihydroxybenzene and their anion and per-trialkylsilyl and stannyl derivatives and their equivalents. Any of various suitable

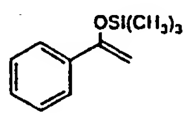
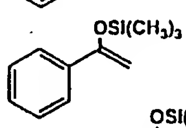
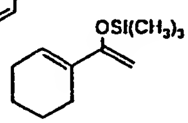
solvents can be used for the glycosylation reaction of which THF, acetone, diethyl ether, methylene chloride, chloroform, and benzene are preferred. The reaction temperature and time can be varied, e.g., ranging from -78° to room temperature for about 0.5 to 12 hours.

The following reactions in a preferred embodiment (Table 1) illustrate the invention.

TABLE 1 - C-Glycosylation



α-epimer β-epimer

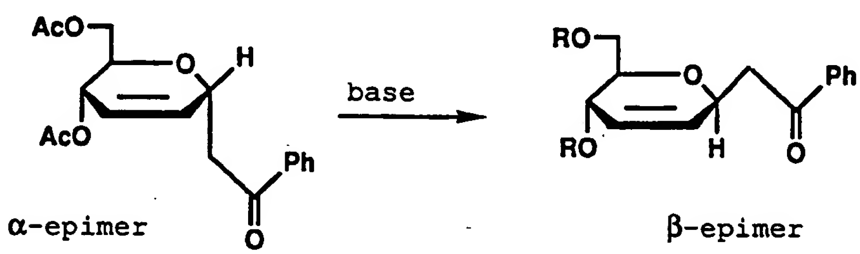
C-Nucleophile	Temperature	Time	Products R	Yield	α:β
$(CH_3)_3SiCH_2CH=CH_2$	-60°C to RT	Overnight	$-CH_2CH=CH_2$	70%	>20:1
$(CH_3)_3SiC{\equiv}N$	-78°C	2 h	$-C{\equiv}N$	75%	3:1
$(CH_3)_3SiC{\equiv}N$	-60°C	1 h	$-C{\equiv}N$	78%	1:3
	-78°C	2 h	$-CH_2C(=O)-Ph$	65%	6:1
	-50°C to RT	12 h	$-CH_2C(=O)-Ph$	78%	2.7:1
	-50°C to 0°C	2 h	2-oxocy-clohexyl	65%	4:1

RT = room temperature

As shown in the table, the epimeric ratio as well as preference for one of the two epimers of the C-glycosylated products is dependent on the temperature of the reaction (see the cases of trimethylsilyl cyanide and acetophenone trimethylsilyl ether). Moreover, quite

significantly, the thermodynamically more favored β-epimer obtained from ketone enol silyl ethers can be obtained as a major product upon treatment of the initial α-epimer enriched product mixture with acid (as described by Kende, A.S.; Fujii, Y. *Tetrahedron Lett.* 1991, 32, 2199-2202) or base (as described by Dawe, R.D.; Fraser-Reid, B. *J.C.S.Chem.Commun.* 1981, 1180-1181 incorporated by reference) (see Scheme 1 below). The present invention in one preferred aspect includes the treatment of the α-epimer enriched product mixture with acid or base thus favoring the yield in the present method of the β-epimer, and making the present C-glycosylation even more versatile. Many of the present C-glycosylated products, particularly those with 1β-carbon chains are key intermediates in the synthesis of various C-glycoside antibiotics (as described in the two reviews cited above, incorporated herewith by reference).

SCHEME 1



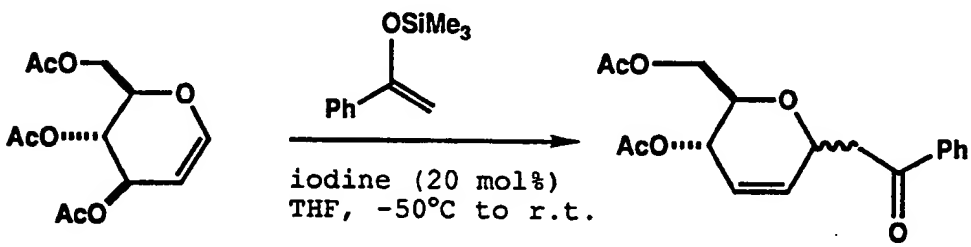
In another preferred aspect, the invention concerns partly and completely deacylated products having enhanced water-solubility, produced by hydrolysis of one or more acyl groups from the acylated product. For hydrolysis, acyl group removal can be achieved for example by refluxing the acylated product, under per se commonly used conditions for hydrolysis and workup, with an aqueous metal hydroxide (MOH; M = Li, K, Na) in methanol or

ethanol, or with Zn $(OAc)_2 \cdot 2H_2O$ in methanol, or with $LiAlH_4$ or diisobutylaluminum hydride in benzene, toluene, ether or THF.

The invention and the best mode of carrying out the same are illustrated by the following non-limitative examples.

Example I

Reaction of Triacetyl D-Glucal With Acetophenone Enol Trimethylsilyl Ether



Triacetyl D-glucal (1.98 mmol) and iodine (0.398 mmol) were dissolved in 10 mL of THF and the solution was cooled to -50°C. To this solution was added acetophenone enol trimethylsilyl ether (2.00 mmol) and the reaction mixture was allowed to warm slowly to room temperature over 12 hours. The reaction mixture was then diluted with 50 mL of ether and the resulting solution was washed with 10 mL of 10% aqueous $Na_2S_2O_3$. The aqueous layer was back-extracted with ether (3 x 10 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated in vacuo. The crude product thus obtained was purified by silica gel flash column chromatography (gradient elution with 9/1 to 2/1 hexanes/ethyl acetate), providing 1.55 mmol of the C-glycosylated product (78%) as a mixture of C-1 epimers (2.7 : 1 α:β). For the major product α-epimer: ^1H NMR (300 MHz; $CDCl_3$) δ 2.03 (s,3H), 2.09 (s,3H), 3.15 and 3.48 (AB quartet, 2H, J_{AB} = 16.4 Hz; the 3.15 and 3.48 ppm peaks are further split into doublets

with J = 6.5 Hz and 7.1 Hz, respectively), 4.13 and 4.25 (AB quartet, 2H, J_{AB} = 11.9 Hz; the 4.13 and 4.25 ppm peaks are further split into doublets with J = 3.6 Hz and 6.6 Hz, respectively), 4.91-4.97 (m,1H), 5.13-5.17 (m,1H), 5.85 and 6.08 (AB quartet, 2H, J_{AB} = 10.4 Hz; the 5.85 and 6.08 ppm peaks are further split into dd with J = 3.0, 2.0 Hz and 2.5, 1.5 Hz, respectively). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 20.70 (q), 21.05 (q), 42.70 (t), 63.25 (t), 65.51 (d), 68.99 (d), 71.04 (d), 124.84 (d), 128.90 (d), 129.38 (d), 133.56 (d), 133.96 (d), 137.98 (d), 137.98 (s), 171.03 (s), 171.42 (s), 197.99 (s).

Example II

Reaction of Triacetyl D-Glucal With Allyltrimethylsilane

The procedure of Example I was followed except that the reaction was initiated at -60°C and the reaction mixture was left at room temperature overnight. The 1-allyl product was obtained in 70% yield with over 20:1 α/β stereoselectivity. For the major α-epimer: ^1H NMR (300 MHz; $CDCl_3$) δ 2.08 (s,6H), 2.27-2.36 (m,1H), 2.41-2.52 (m,1H), 3.93-4.02 (m,1H), 4.15 and 4.23 (AB quartet, 2H, J_{AB} = 11.9 Hz; the 4.15 and 4.21 ppm peaks are further split into doublets of doublets with J = 3.5 and 6.6 Hz, respectively), 4.25-4.31 (m,1H), 5.09-5.17 (m,3H), 5.76-5.89 (m,1H), 5.79 and 5.93 (AB quartet, 2H, J_{AB} = 10.4 Hz; the 5.79 and 5.93 ppm peaks are further split into dd with J = 2.8, 1.9 and 2.4, 1.6 Hz, respectively); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 20.73, 21.00, 37.96, 62.94, 65.13, 70.00, 71.35, 117.44, 123.75, 132.83, 133.97, 170.24, 170.55.

Example III

Reaction of Triacetyl D-Glucal With 1-Trimethylsilyloxy-1-cyclohexene

The procedure of Example I was followed except

that the reaction was performed at -78°C for 2 hours. The 1-(2-oxocyclohexyl) product was obtained in 65% yield with over 4:1 α/β stereoselectivity. For the major α-epimer: ^1H NMR (360 MHz; $CDCl_3$) δ 2.08 (a,3H), 2.11 (s,3H), 2.30-2.43 (m,3H), 2.61-2.65 (m,1H), 3.86 (ddd, 1H, J = 6.7, 6.7, 3.6 Hz), 4.16 and 4.24 (AB quartet, 2H, J_{AB} = 11.9 Hz; the 4.16 and 4.24 ppm peaks are further split into doublets with J = 3.6 and 6.8 Hz, respectively), 4.46 (ddd, 1H, J = 8.8, 4.5, 2.3 Hz), 5.11-5.16 (m,1H), 5.77 and 6.14 (AB quartet, 2H, J_{AB} = 10.5 Hz; the 5.77 and 6.14 ppm peaks are further split into doublets of doublets with J = 2.9, 2.0 and 2.7, 1.5 Hz, respectively); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 20.82, 21.06, 24.67, 27.94, 30.30, 42.74, 53.41, 62.92, 65.04, 70.15, 70.27, 123.56, 133.06, 170.34, 170.75, 210.95.

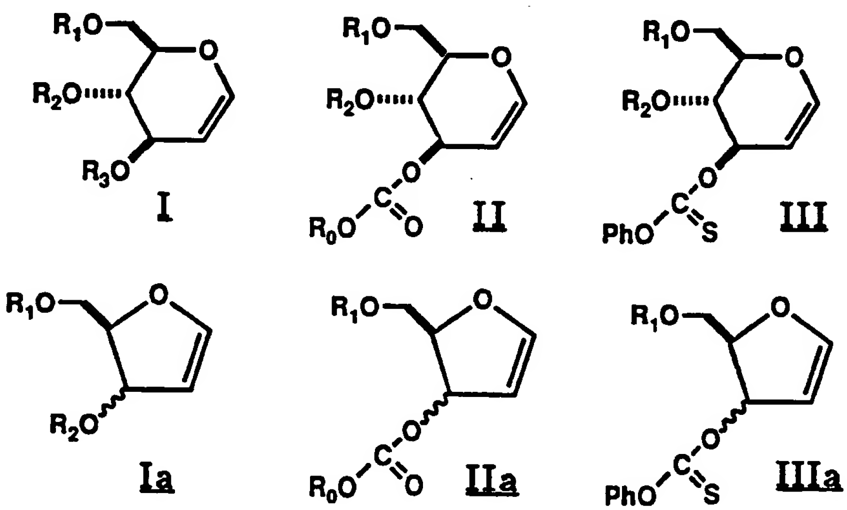
The procedure of Example 1 can be used for preparation of the stereoselective 2,3,5-triacetylribosylation of acid-sensitive substrate compounds such as precursors of the known compounds showdomycin, ravidomycin, formycin and like pharmacologically useful compounds. For example, the synthesis of glycosylated showdomycin can be accomplished using the commercially available soft carbon nucleophile 1,2 bis(trimethylsilyl)oxy-1-cyclobutene for stereoselective addition of a glycal selected from glycals of formula I-III and Ia-IIIa to produce an adduct which is converted to the target compound which can be deacylated by per se known procedures to provide showdomycin. A similar synthesis is reported in the Hacksell and Daves review article, supra, at page 43. The resulting novel triacetylglycosylated substrate compounds can as indicated be partly or completely deacylated to the novel glycosylated substrate compounds which are contemplated to have substantial advantage with respect to greater water solubility and yet

have substantially the same useful antineoplastic activity and posology as the known compounds.

Having described the invention, the embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

Claims

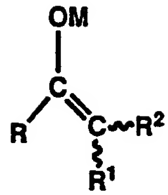
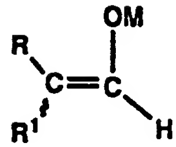
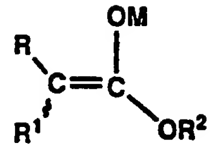
1. C-1α and C-1β glycoside epimer compounds obtained by reacting a soft carbon nucleophile compound and a glycosylating agent selected from acylated, carbonated and thionocarbonated five- and six-membered glycals of the formulas I, II and III and Ia, IIa and IIIa

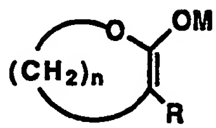
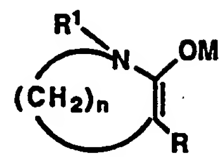
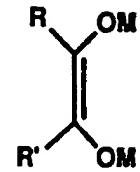


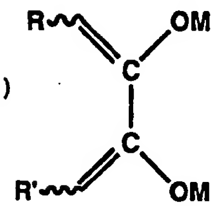
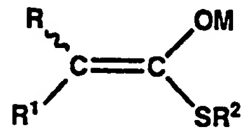
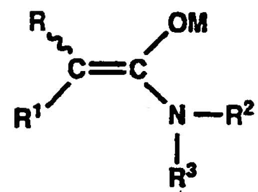
I II III Ia IIa IIIa

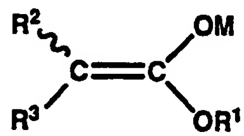
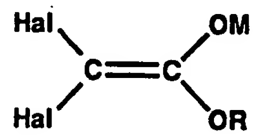
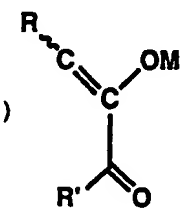
where R_0 is a lower alkyl group and R_1, R_2 and R_3 are the same or different and represent an aliphatic acyl group or aromatic acyl group, in the presence of a catalytic amount of iodine to provide a reaction mixture containing the corresponding C-1α and C-1β glycosylated C-glycoside epimers, isolating at least one or both of said α and β epimers stereoselectively from said mixture, and optionally removing one or more acyl groups from said epimer products.

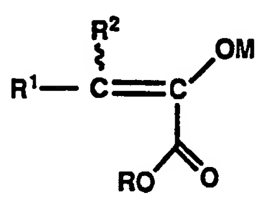
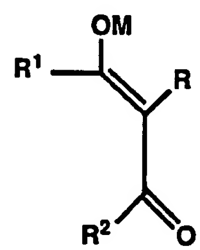
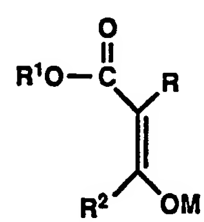
2. C-Glycoside products according to claim 1 wherein the soft carbon nucleophile comprises a compound or a moiety selected from members of the group consisting of enolate derivatives having the formulas a) to w)

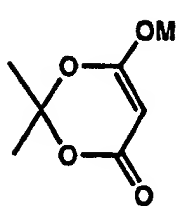
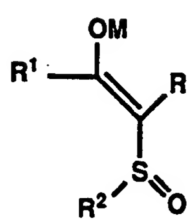
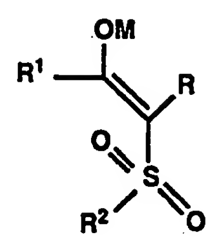
a)  ; b)  ; c)  ;

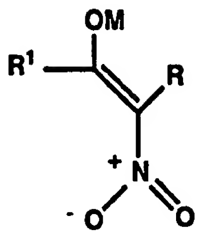
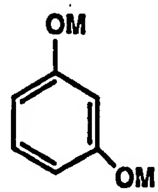
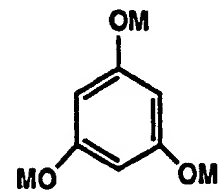
d)  ; e)  ; f)  ;

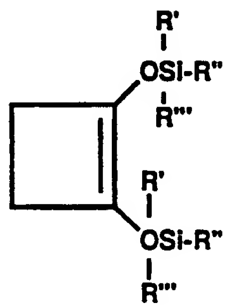
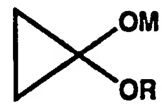
g)  ; h)  ; i)  ;

j)  ; k)  ; l)  ;

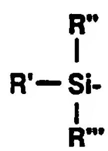
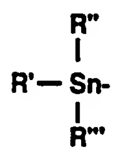
m)  ; n)  ; o)  ;

p)  ; q)  ; r)  ;

s)  ; t)  ; u)  ;

v)  ; and w)  ;

and allyl, vinyl, alkynyl and propargyl silanes and stannanes, and MCN; wherein M represents

 or  ,

R, R^1 and R^2 are independently selected from alkyl, aryl, alkenyl and alkynyl, n is from 1 to 5, Hal is a halogen atom, and R′, R″ and R′″ are independently selected from lower alkyl groups.

3. A product according to claim 2 wherein the nucleophile is acetophenone enol trimethylsilyl ether.

4. A product according to claim 2 wherein the nucleophile is allyltrimethylsilane.

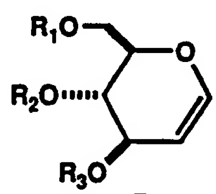
5. A product according to claim 2 wherein the nucleophile is trimethylsilyloxy-1-cyclohexane.

6. A product according to claim 2 wherein the nucleophile is a showdomycin aglycon or its precursor.

7. A product according to claim 2 wherein the nucleophile is a ravidomycin aglycon or its precursor.

8. A product according to claim 2 wherein the nucleophile is a formycin aglycon or its precursor.

9. A process for preparing C-1α and C-1β glycoside epimer compounds comprising reacting a soft carbon enolate nucleophile and a glycal selected from acylated, carbonated and thionocarbonated five- and six-membered glycals of the formulas I, II and III and Ia, IIa and IIIa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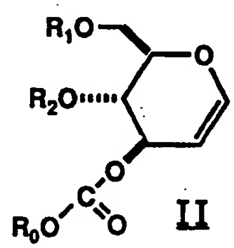
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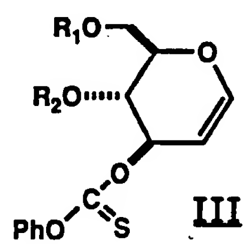
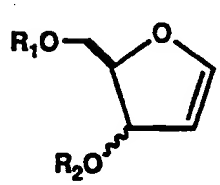
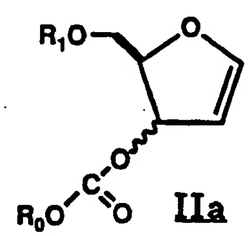
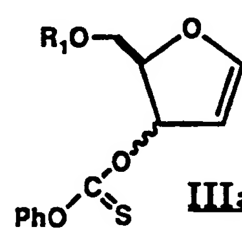

III

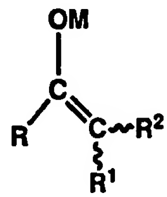
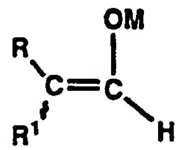
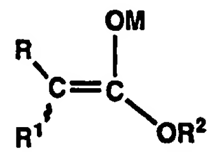

Ia

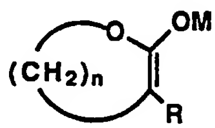
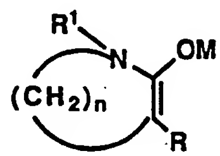
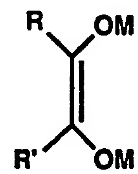

IIa

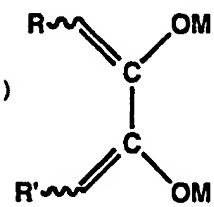
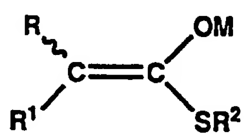
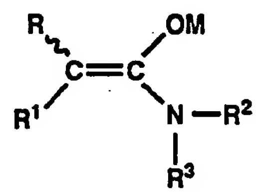

IIIa

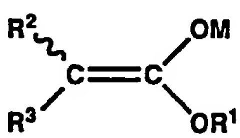
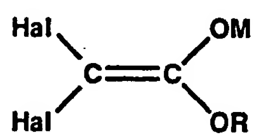
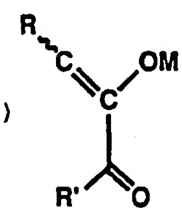
where R_0 is a lower alkyl group and R_1, R_2 and R_3 are the same or different and represent an aliphatic acyl group or aromatic acyl group, in the presence of a catalytic amount of iodine to provide a reaction mixture containing the corresponding C-1α and C-1β glycosylated C-glycoside epimers, and isolating at least one or both of said α and β epimers stereoselectively from said mixture, and optionally removing one or more acyl groups from said epimer products.

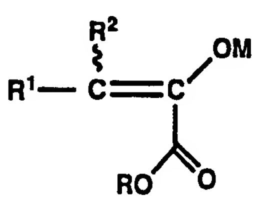
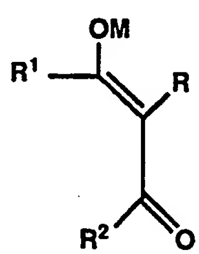
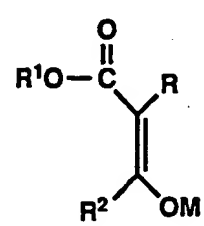
10. A process according to claim 9 wherein the soft carbon nucleophile comprises a compound or a moiety selected from the group consisting of enolate derivatives having the formulas a) to w)

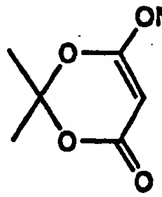
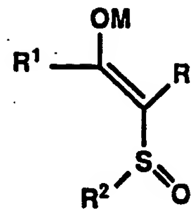
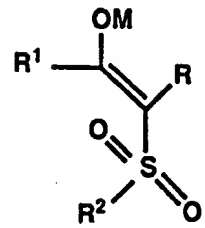
a)  ; b)  ; c)  ;

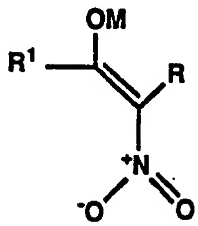
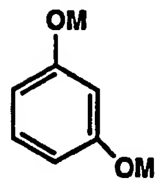
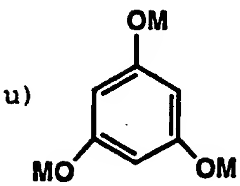
d)  ; e)  ; f)  ;

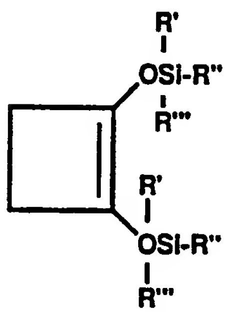
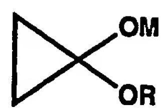
g)  ; h)  ; i)  ;

j)  ; k)  ; l)  ;

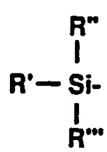
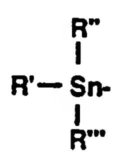
m)  ; n)  ; o)  ;

p)  ; q)  ; r)  ;

s)  ; t)  ; u)  ;

v)  ; and w)  ;

and allyl, vinyl, alkynyl and propargyl silanes and stannanes, and MCN; wherein M represents

 or  ,

R, R^1 and R^2 are independently selected from alkyl, aryl, alkenyl and alkynyl, n is from 1 to 5, Hal is a halogen atom, and R′, R″ and R‴ are independently selected from lower alkyl groups.

11. A process according to claim 10 wherein the glycal is a tri-acyl D-glucal.

12. A process according to claim 10 wherein the

soft carbon nucleophile contains an acid-labile structural unit.

13. A process according to claim 10 comprising the step of treating said reaction mixture containing α and β epimers with acid or base to convert the α epimer to β epimer thereby increasing the yield of said β epimer in the reaction mixture.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09037

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07H 1/00, 3/00, 15/00, 15/24; C08B 37/06; C07G 3/00
US CL :536/1.11, 4.1, 6.4, 18.6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/1.11, 4.1, 6.4, 18.6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,713,447 (Letton) 15 December 1987, see entire document.	1-13
A	US, A, 4,871,837 (Magnusson et al) 03 October 1989, see entire document.	1-13
A	US, A, 5,003,057 (McCurry et al) 26 March 1991, see entire document.	1-13
A	Progress in Medicinal Chemistry, Vol. 22, issued 1985, U. Hacksell et al., "I The Chemistry and Biochemistry of C-Nucleosides and C-Argylglycosides", pages 1-65, see entire document.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 1993	30 DEC 1993

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	D. Kyza for DR. HERBERT J. LILLING
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ACC Chem. Res., Vol. 23, No. 6, issued 1990, G.D. Daves Jr., "C-Glycoside Synthesis by Palladium-Mediated Glycal-Aglycon Coupling Reactions", pages 201-206, see entire document.	1-13
A	J.C.S.Chem Comm., issued 1981, R.D. Dawe et, al., "Alpha-C-Glycopyranoides from Lewis Acid Catalyzed Condensations of Acetylated Glycals and Enol Silanes", pages 1180-81, see entire document.	1-13
A	Tetrahedron Letters, Vol. 30, No. 46, issued 1989, Sabol et al., "Conformationally Restricted Leukotriene Antagonists. Synthesis of Some Leukotriene D_4 Analogs from D-Xylose", pages 6271-74, see entire document.	1-13
A	Tetrahedron Letters, Vol. 25, No. 49, issued 1984, J. Herscovici et al., "Olefin Addition to Acetylated Glycals. A New Route to C-Glycosides", pages 5653-56, see entire document.	1-13
A	J. Org. Chem., Vol. 48, No. 17, issued 1983, U. Hacksell et al., "Stereocontrolled Palladium (II)-Mediated Coupling of Furanoid Glycals with a Pyrimidinylmercuric Salt. Facile C-Nucleoside Syntheses", pages 2870-2876, see entire document.	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09037

Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(Form PCT/ISA/206 Previously Mailed.)
Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-13, formula I with the enolate derivative (a).

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1-13, drawn to the product and process for preparing the first epimer compounds represented by Formula I with the enolate derivative represented by the first member (a).

In view of the fact that each of the additional products and each of the additional processes may be separated, this Examiner will examine each of the products with the processes in order to half the total number of inventions.

II. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with b.

III. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with c.

IV. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with d.

V. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with e.

VI. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with f.

VI. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with g.

VII Claims 1-13, drawn to the product and process of preparing the product represented by formula I with h.

VIII. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with i.

IX. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with j.

X. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with k.

11. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with l.

12. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with m.

13. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with n.

14. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with o.

15. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with p.

16. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with q.

17. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with r.

18. Claims 1-13, drawn to the product and process of preparing the product represented by formula I

with s.

19. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with t.

20. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with u.

21. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with v.

22. Claims 1-13, drawn to the product and process of preparing the product represented by formula I with w.

23. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with a.

24. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with b.

25. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with c.

26. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with d.

27. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with e.

28. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with f.

39. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with g.

30. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with h.

31. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with i.

32. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with j.

33. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with k.

34. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with l.

35. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with m.

36. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with n.

37. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with o.

38. Claims 1-13, drawn to the product and process of preparing the product represented by formula II

with p.

39. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with q.

40. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with r.

41. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with s.

42. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with t.

43. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with u.

44. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with v.

45. Claims 1-13, drawn to the product and process of preparing the product represented by formula II with w.

46. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with a.

47. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with b.

48. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with c.

49. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with d.

50. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with e.

51. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with f.

52. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with g.

53. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with h.

54. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with i.

55. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with j.

56. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with k.

57. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with l.

58. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with m.

59. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with n.

60. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with o.

61. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with p.

62. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with q.

63. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with r.

64. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with s.

65. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with t.

66. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with u.

67 Claims 1-13, drawn to the product and process of preparing the product represented by formula III with v.

68. Claims 1-13, drawn to the product and process of preparing the product represented by formula III with w.